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KIDNEY DISEASE IN AGING

Haruhisa Otani and **Masatoshi Mune**
Third Dept. of Internal Medicine
Wakayama Medical College, Japan

ABSTRACT

There is an increasing number of elderly patients with glomerulonephritis. A number of reports regarding renal function [1-9] and morphology [10-13] in aged people have been published. However, few studies have been reported on the effect of glomerulonephritis on the kidneys of aged patients. Recently, some articles concerning renal function and histological changes in aged nephritic patients were reported [14]. Several reports about the effects of aging in an experimental kidney disease model [15-23] and on cultured renal cells [22, 24, 25] have been published. This review will focus mainly on the mechanisms of the decrease in renal function and morphological changes with aging.

Changes in Renal Function with Aging

Changes in Glomerular Filtration Rate (GFR) and Renal Plasma Flow (RPF) with Aging

Several studies have been reported showing an age-related decline in renal function after age 30-40 years [1]. Rowe et al. reported the results from the Baltimore Longitudinal Study on Aging, which demonstrated an age-related decline in creatinine clearance (Ccr) in normal subjects who were followed over a 10-year period [2]. Mean Ccr decreased from 140 mL/min/1.73 m^2 at age 25-34 y to 97 mL/min/1.73 m^2 at age 75-84 y. A subsequent report from this longitudinal study indicates that Ccr declines at an annual rate of approximately 0.87 mL/min/1.73 m^2 [3]. However, one third of the subjects had no decrease in Ccr. Recently, Fliser et al. [4-6] showed that in healthy elderly, GFR (by insulin clearance), although lower than in younger individuals, is mostly within the normal range.

The effective renal plasma flow (ERPF), estimated by measuring p-aminohippuric acid (PAH) clearance, was shown to decrease from a mean of 649 mL/min during fourth decade to a mean of 289 mL/min during the ninth decade [7]. ERPF is reduced more than GFR [4]. Then, filtration fraction (FF) is increased [5]. The decrease in RPF with aging is due to either intraluminal vascular pathology or an increased renal vascular resistance caused by vasoconstriction [1].

To whom all correspondence should be addressed:
Dr. Masatoshi Mune; Third Dept. of Internal Medicine; Wakayama Medical College; 27 Nanabancho, Wakayama, 640, Japan

Changes in Concentrating and Diluting Ability

A decrease in concentrating ability with age is well documented. Analysis of the Baltimore Longitudinal Study on Aging revealed that twelve hours of water deprivation increased mean urine osmolality to 1,109 mosm/kg H_2O in young subjects, 1,051 mosm/kg H_2O in middle-aged subjects, and 882 mosm/kg H_2O in old subjects [8]. Maximum diluting ability, as measured by minimum urine osmolality achieved with water loading, also decreased with age [9].

Morphological Change in Kidneys with Aging

The incidence of sclerotic glomeruli increases with advancing age, from less than 5% of the total glomeruli at age 40 to 10-30 % of the total by the eighth decade [10]. Kasiske reported a direct correlation between the number of sclerotic glomeruli and the severity of atherosclerosis [11]. It has been suggested that age-associated glomerulosclerosis is mainly due to ischemic obsolescence of glomeruli. The course of this ischemic obsolescence of glomeruli has been provided by several investigators [12-13]. Progressive collapse of the glomerular tuft occurs with wrinkling of the basement membrane. This is followed by simplification and reduction in the vascular channels. Deposition of hyaline occurs in both the residual glomerular tuft and the space of Bowman's capsule, leading to the rapid disappearance of identifiable structures. The obsolescent glomerulus may be reabsorbed and disappear entirely.

Age-Related Changes in the Kidneys of Patients with Glomerulonephritis

The effect of aging on renal functions and morphology in healthy subjects are well documented, as mentioned above. However, little is known about the effects of aging on the kidneys of patients with glomerulonephritis. Suzuki and Arakawa reported the renal function and histological changes in 962 patients with mild mesangial proliferative glomerulonephritis (MesPGN), whose age ranged from 7 to 82 years old. GFR and RPF were significantly lower in nephritic patients than in normal subjects [14]. Age-related decreases of GFR, RPF, and maximal urine specific gravity, measured by Fishberg concentration test, were found in both groups. Serum levels of creatinine, urea nitrogen, and uric acid were significantly higher in nephritic patients than in the normal population. Age-related increases of those

parameters were found in both groups. Although the incidence of sclerotic glomeruli was almost same as that of the normal population, the incidence of athero-arteriolosclerosis was higher than that of normal subjects. Thus, athero-arteriolosclerosis seems to be more age-dependent than glomerulosclerosis in patients with mild MesPGN.

Mechanisms of the Decrease in Renal Function or Morphological Changes with Aging

Aging Effects on Mesangial Cell Functions

Changes in the Proliferation of Mesangial Cell

Mesangial cell proliferation is a common manifestation in various types of glomerular disease and is considered to play a key role in the pathogenesis of glomerular sclerosis. Several studies have suggested a link between glomerular hypercellularity and increases in the extracellular matrix (ECM) [26]. However, little is known about mesangial cell proliferation in aged patients with renal disease. It is difficult to investigate the aging effect on pure mesangial cell proliferation in patients with renal disease because of the influence of other aging events such as atherosclerosis. Recently, several animal experiments assessing the aging effect on the proliferation of mesangial cell have been reported.

Pugliese et al. investigated the proliferative function of cultured mesangial cells from rats of the Milan normotensive strain (MNS) and the Milan hypertensive strain (MHS) [24] . MNS rats and MHS rats are genetically related, but spontaneous glomerulosclerosis occurs in MNS and not in MHS rats. Fetal bovine serum-stimulated cell growth rate in mesangial cells from MNS rats was increased with aging. However, the cell growth rate of mesangial cells from MHS rats decreased with aging. The investigators concluded that the age-associated decline in the proliferative activity of mesangial cells from MHS animals could actually reflect a normal process of cell aging, which may offer protection from the occurrence of glomerulosclerosis. Age-dependent hyperresponsiveness of mesangial cells to growth stimuli in MNS rats may facilitate the development of glomerulosclerosis.

Glomerular cell proliferative function in Fischer 344 rats, which display focal and diffuse glomerulosclerosis with aging, has also been reported [15]. Proteinuria, glomerular basement membrane widths, and fractional mesangial volumes were found to increase with aging. Glomerular proliferating cell nuclear antigen (PCNA) staining remained positive at old age (24 months). Also, primary cultured mesangial cells from different age groups were studied in parallel. Cultured mesangial cell Ca++ signaling and contraction to vasopressin were unchanged with aging. The researchers concluded that continued growth is associated with the glomerulosclerosis of aging.

The proportion of cells in various phases of the cell cycle from the kidneys of young (5 mo) and old (20 mo) Fischer 344 rats was investigated using flow cytometry [25]. The percentage of S-phase cells in the kidney decreased in old rats when compared with young rats, regardless of treatment conditions, indicating a parallel decline in cell proliferating activity with aging.

Male Munich-Wistar rats (MWF/Ztm) spontaneously develop proteinuria and glomerulosclerosis with aging [16]. Morphometric analysis showed an important increase in glomerular volume with aging. This glomerular tuft enlargement was the result of an increase in the number of glomerular cells and a concomitant increase in cell volume, suggesting that glomerular cell growth is related to age-dependent glomerulosclerosis.

We investigated the effect of aging on mesangial cell proliferation using a mesangioproliferative nephritis model of anti-Thy 1 nephritis [unpublished data]. Brown Norway/Fisher 344 F1 hybrid rats (BN/F344 rat) were used as an experimental animal model to investigate the effects of aging on renal morphology and mesangial cell function in experimental glomerulonephritis. The BN/F344 strain is considered to be an appropriate model for this study because of its resistance to spontaneous glomerulosclerosis. In this model, a single injection of anti-Thy 1 antibody results in rapid, complement-dependent loss of mesangial cells with disruption of the mesangial matrix ("mesangiolysis") [27, 28]. The early mesangiolysis at day 1-2 is followed by marked mesangial cell proliferation at day 4, becoming prominent at 1-2 weeks. Mesangial cell proliferation in this model is stimulated by growth factors from infiltrated monocyte/macrophages after the injury of mesangial cells. Our data showed that mesangial cell proliferation in aged rats was not as prominent as in young rats at day 6. The glomerular cell number in aged rats at day 2 decreased to same extent as in young rats. This observation suggests that mesangial cell proliferation in old rats was suppressed even though mesangial cells were injured to almost the same extent in young and old rats at an early period. The suppression of mesangial cell proliferation is possibly due to the deterioration of the proliferative ability of mesangial cells in old rats. Decreased mesangial cell proliferative response in aged BN/F344 rats may contribute to this strain's resistance to glomerulosclerosis. It has been suggested that other rat strains such as the MNS may show increased mesangial cell proliferation in anti-Thy-1 nephritis with age.

Changes of Mesangial Matrix

Age-related changes in glomerular volume and hydroxyproline content in rats and humans were investigated [17]. Rat glomerular size increased seven-fold between 5 week and 2 years of age. When 4-hydroxyproline contents were expressed as weight of basement membrane/mesangial matrix material, it was found that basement membrane/mesangial matrix material content per glomerulus markedly increased with age (12-fold). However, when expressed per unit volume, this change was greatly reduced (2-fold). Therefore, a greater glomerular size, in itself, does not accelerate the rate of basement membrane/mesangial matrix material deposition.

Human glomeruli increased seven-fold in size from infancy to adulthood and then decreased during senescence. Basement membrane/mesangial matrix material content varies little from infancy to senescence if expressed per unit of glomerular volume.

Ueda et al. investigated the age-related changes in the anionic sites of the mesangial matrix in rats, employing polyethyleneimine (PEI) as a cationic probe [18]. They compared the numbers of anionic sites detected by the immersion method and by intravenous administration of PEI. The number of PEI particles in the mesangial matrix significantly decreased with aging in both methods. Loss of negative charge in the mesangial matrix is believed to promote mesangial dysfunction and the entrapment of macromolecular substances, suggesting an important role in the onset of glomerular sclerosis. However, Duan et al. reported that glomerular anionic sites were not significantly altered in aged ddY mice [19]. Progressive increase in glomerular extracellular matrices, including thickening of the glomerular basement membrane (GBM), formation of GBM nodules, and mesangial matrix increase, was considered to be the primary age-related ultrastructural change in aging mice.

The relationship of age-related changes in renal function and structure to changes in glomerular proteinase activities was reported by Schaefer et al. [20]. GFR declined significantly in aged Wistar rats while albuminuria increased almost 10-fold. The glomerular protein to DNA ratio increased by almost 70%, suggesting deposition of mesangial matrix within the glomerulus. These structural changes were associated with reduction in glomerular cysteine proteinase and metalloproteinase activities in the adolescent and older animals. These alterations of proteolytic enzyme activities in the aged rat kidney correspond well with the enhanced deposition of glomerular matrix. This study suggested a causal involvement of renal cysteine proteinase and metalloproteinase in the protein accumulation of the aged rat kidney.

Aging Effect on Interstitial Fibrosis

Peleg et al. reported that cortex and outer medulla of kidneys of old rats expressed significantly higher percentage of the mRNA for type I collagen, the major structural constituent of fibrotic tissues, compared to the respective regions in the young rat kidneys [21]. Their study also indicated a close relationship between the expression of the mRNA for type I collagen and the deposition of collagen in both the cortex and outer medulla of the kidney. These findings might explain some of the kidney impairments caused by fibrosis during senescence .

Reactive Oxygen Species (ROS) Mechanism for Kidney Injury in Aging

The importance of the oxidant/antioxidant balance in the process of age-related glomerular sclerosis (GS) was reported by Ruiz-Torres et al. [22]. Old Fisher 344 rats showed increased urinary protein excretion and augmented protein glomerular content, an indirect index of GS. Isolated glomeruli from these rats produced elevated amounts of superoxide anion and hydrogen peroxide, and catalase activity was also increased. The glomerular thiobarbituric acid-reactive substances (TBARS) content was higher in old rats than in young rats. Similar results were also obtained in cultured mesangial cells.

Another Mechanism for Kidney Injury in Aging

The effects of aging and dietary protein on the L-arginine-nitric oxide (NO) pathway and the progress of chronic nephropathy in Fischer 344 rats were examined [23]. Old rats fed a 23% protein diet showed highly progressive nephropathy and decreased urinary excretion of nitrite/nitrate (NOx), suggesting that an age-related decrease in the synthesis of NO could be associated with the progress of chronic nephropathy.

CONCLUSIONS

Mesangial cell dysfunction, such as continuous cell growth or formation of excess mesangial matrix, is considered to be the key factor in the progress of glomerular sclerosis with aging in some experimental rat models. However, patients with mild MesPGN did not show increased sclerotic glomeruli but did exhibit a greater incidence of athero-arteriosclerotic lesions compared with the normal population [14]. Furthermore, in healthy elderly with fewer athero-arteriosclerotic lesions, GFR has been shown to be mostly within normal range [4-6]. From these observations, it has been suggested that the formation of glomerulosclerosis is not accelerated with aging in humans. Accumulation of detailed analysis of re-biopsy specimens at young and old age will be useful to confirm this hypothesis.

REFERENCES

1. Lindeman, R.D. Overview: Renal physiology and pathophysiology of aging. Am. J. Kidney. Dis., 16: 275-282, 1990.
2. Rowe, J.W., Anders, R., Tobin, J.D., Norris, A.H., and Shock, N.W. The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. J. Gerontol., 31: 155-163, 1976.
3. Lindeman, R.D., Tobin, J.D., and Shock, N.W. Longitudinal studies on the rate of decline in renal function with age. J. Am. Geriatr. Soc., 33: 278-285, 1985.
4. Fliser, D., Zeier, M., Nowack, R., and Ritz, E. Renal functional reserve in healthy elderly people. J. Am. Soc. Nephrol., 3: 1371-1377, 1993.
5. Fliser, D., Franek, E., Joest, M., Block, S., Mutschler, E., and Ritz, E. Changes of renal function in the elderly-influence of hypertension and cardiac function. Kidney Int., 51: 1196-1204, 1997.

6. Fliser, D., Franek, E., and Ritz, E.: Renal function in the elderly: Is the dogma of an inexorable decline of renal function correct? Nephrol. Dial. Transplant, 12: 1553-1555, 1997.

7. Davies, D.F., and Shock, N.W. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J. Clin. Invest., 29: 496-507, 1950.

8. Rowe, J.W., Shock, N.W., and DeFronzo, R.A. The influence of age on the renal response to water deprivation in man. Nephron, 17: 270-278, 1976.

9. Lindeman, R.D., Lee, T.D. Jr., Yiengst, M.J., and Shock, N.W. Influence of age, renal disease, hypertension, diuretics and calcium on the antidiuretic response to suboptimal infusions of vasopressin. J. Lab. Clin. Med., 68: 206-223, 1966.

10. Kaplan, C., Pasternack, B., Shah, H., and Gallo, G. Age-related incidence of sclerotic glomeruli in human kidneys. Am. J. Pathol., 80: 227-234, 1975.

11. Kasiske, B.L. Relationship between vascular disease and age-associated changes in the human kidney. Kidney Int., 31: 1153-1159, 1987.

12. McManus, J.F.A., and Lupton, C.H. Jr. Ischemic obsolescence of renal glomeruli. Lab. Invest.,9: 413-434, 1960.

13. Takazakura, E., Sawabu, N., Handa, A., Takada, A., Shinoda, A., and Takeuchi, J. Intrarenal vascular changes with age and disease. Kidney Int., 2: 224-230, 1972.

14. Suzuki, S. and Arakawa, M. Age-related changes in the kidney of patients with mild mesangial proliferative glomerulonephritis[JAPANESE]. Jpn. J. Geriatrics, 28: 311-317, 1991.

15. McDermott, G.F., Ingram, A., Scholey, J., Kirkland, J.L., and Whiteside, C.I. Glomerular dysfunction in the aging Fischer 344 rat is associated with excessive growth and normal mesangial cell function. J. Gerontol. Series A, Biological Sciences & Medical Sciences 51: M80-85, 1996.

16. Remuzzi, A., Puntorieri, S., Alfano, M., Macconi, D., Abbate, M., Bertani, T., and Remuzzi, G. Pathophysiologic implications of proteinuria in rat model of progressive glomerular injury. Lab. Invest., 67: 572-579, 1992.

17. Cortes, P., Zhao, X., Dumler, F., Tilley, B.C., and Atherton, J. Age-related changes in glomerular volume and hydroxyproline content in rat and human. J. Am. Soc. Nephrol., 2: 1716-1725, 1992.

18. Ueda, Y., Ono, Y., Sagiya, A., Ishitobi, F., Takimoto, T., Hirabayashi, K. Oka, K., Kanaya, H., and Iidaka, K. Changes of anionic sites in the mesangium with aging in rats: a comparison of the immersion and intravenous PEI methods. Jpn. J. Nephrol. 33: 825-829, 1991.

19. Duan, H.J. and Nagata, T. Glomerular extracellular matrices and anionic sites in aging ddY mice: a morphometric study. Histochemistry 99: 241-249, 1993.

20. Schaefer, L., Teschner, M., Ling, H., Oldakowska, U., Heidland, A., and Schaefer, R.M. The aging rat kidney displays low glomerular and tubular proteinase activities. Am. J. Kidney Dis., 24: 499-504, 1994.

21. Pleg, I., Greenfeld, Z., Cooperman, H., and Shoshan, S. Type I and type III collagen mRNA levels in kidney regions of old and young rats. Matrix, 13: 281-287, 1993.

22. Ruiz-Torres, P., Lucio, J., Gonzalez-Rubio, M., Rodriguez-Puyol, M., and Rodriguez-Puyol, D. Oxidant/antioxidant balance in isolated glomeruli and cultured mesangial cells. Free Radical Biology & Medicine, 22: 49-56, 1997.

23. Sonaka, I., Futami, Y., and Maki, T. L-arginine-nitric oxide pathway and chronic nephropathy in aged rats. J. Gerontol., 49: B157-61, 1994.

24. Pugliese, F., Ferrario, R.G., Ciavolella, A., Tamburin, M., Benatti, L., Casini, A., Pastrono, C., and Salvati, P. Growth abnormalities in cultured mesangial cells from rats with spontaneous glomerulosclerosis. Kidney Int., 47: 106-113, 1995.

25. Lu, M.H., Hinson, W.G., Turturro, A., Anson, J., and Hart, R.W. Cell cycle analysis in bone marrow and kidney tissues of dietary restricted rats. Mechanism of Ageing & Development, 59: 11-121, 1991.

26. Eng, E., Floege, J., Young, B.A., Couser, W.G., and Johnson, R.J. Does extracellular matrix expansion in glomerular disease require mesangial cell proliferation? kidney Int., 45: s45-47, 1994.

27. Ishizaki, M., Masuda, Y., Fukuda, Y., Sugisaki, Y., Yamanaka, N., and Masugi, Y. Experimental mesangio- proliferative glomerulonephritis in rats induced by intravenous administration of anti-thymocyte serum. Acta. Pathol. Jpn., 36: 1191-1203, 1986.

28. Yamamoto, T. and Wilson, C.B. Quantitative and qualitative studies of antibody-induced mesangial cell damage in the rat. Kidney Int., 32: 514-525, 1987.